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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/656,309	09/06/2000	Walter Callen	DIVER1350-2	9418

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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	16

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/656,309	CALLEN ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-42 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *31-42 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *06 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendment of the specification, amendment of claims 31 and 32, cancellation of claims 1-30 and 43-51 and addition of new claim 52, Paper No. 14, 7/26/2002, is acknowledged. Claims 31-42 and 52 are at issue and are present for examination.

Applicants' arguments filed on 7/26/2002, Paper No. 14, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-42 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 (32-42 and 52 dependent on) is indefinite in that it is confusing in the recitation "... obtaining a nucleic acid comprising a sequence as set forth in SEQ ID NO:1, sequences having at least 70% identity thereto, sequences complementary to SEQ ID NO:1 or sequences having at least 70% identity to SEQ ID NO:1,..." The recitation is worded poorly such that it is unclear why applicants refer to those sequences 70% identical to SEQ ID NO:1, twice. If it is applicants intent to claim the

use of sequences complementary to those sequences at least 70% identical to SEQ ID NO:1, then it is suggested that applicants amend this recitation such as "... obtaining a nucleic acid comprising a sequence as set forth in SEQ ID NO:1, sequences having at least 70% identity thereto, and sequences complementary to those sequences having at least 70% identity to SEQ ID NO:1,..." For the purpose of compact prosecution, this is how the claim is interpreted.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-42 and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 31-42 and 52 are directed to all possible methods of generating any variant: comprising obtaining a nucleic acid comprising obtaining a nucleic acid sequence as set forth in SEQ ID NO:1, sequences having at least 70% identity thereto, sequences complementary to SEQ ID NO:1 or sequences having at least 70% identity to SEQ ID NO:1, and fragments comprising at least 30 consecutive nucleotides thereof, and modifying, deleting or adding one or more nucleotides in said sequence (claim 31). The specification, fails to describe the function of such a method, nor the function of any of the variants that would be generated from such a method. There is no disclosure of

any particular structure to function/activity relationship in any disclosed species generated by such a method. The specification also fails to give guidance as which if any residues should be modified by disclosing any identifying structural characteristics or properties of the proposed variant polynucleotides, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 31-42 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating a polymerase variant: comprising obtaining a nucleic acid comprising obtaining a nucleic acid sequence having at least 70% identity to SEQ ID NO:1 and sequences complementary thereto and modifying, deleting or adding one or more nucleotides in said sequence, wherein said variant maintains polymerase activity, does not reasonably provide enablement for any method of generating any variant: comprising obtaining a nucleic acid comprising obtaining a nucleic acid sequence as set forth in SEQ ID NO:1, sequences having at least 70% identity thereto, sequences complementary to SEQ ID NO:1 or sequences having at least 70% identity to SEQ ID NO:1, and fragments comprising at least 30 consecutive nucleotides thereof, and modifying, deleting or adding one or more

nucleotides in said sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 31-42 and 52 are so broad as to encompass any method of generating any variant: comprising obtaining a nucleic acid comprising obtaining a nucleic acid sequence as set forth in SEQ ID NO:1, sequences having at least 70% identity thereto, sequences complementary to SEQ ID NO:1 or sequences having at least 70% identity to SEQ ID NO:1, and fragments comprising at least 30 consecutive nucleotides thereof, and modifying, deleting or adding one or more nucleotides in said sequence. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims, including all methods of generating variant polynucleotides which encode enzymes with polymerase activity as well as those which encode proteins with no function/activity and those which do not encode polypeptides/proteins.

The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural or functional limits generated variants. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to polymerase having the amino acid sequence of SEQ ID NO: 1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all methods of modifications and fragments of any nucleic acid sequence having 70% identity to SEQ ID NO: 1 or fragments comprising at least 30 consecutive nucleotides thereof, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting function/activity; (B) the

general tolerance of SEQ ID NO: 1 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleic acid residue of SEQ ID NO: 1 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to generate desired variant and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those methods of the claimed genus having the desired function.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any method of generating any variant: comprising obtaining a nucleic acid comprising obtaining a nucleic acid sequence as set forth in SEQ ID NO:1, sequences having at least 70% identity thereto, sequences complementary to SEQ ID NO:1 or sequences having at least 70% identity to SEQ ID NO:1, and fragments comprising at least 30 consecutive nucleotides thereof, and modifying, deleting or adding one or more nucleotides in said sequence. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of

having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
October 17, 2002